

REMARKS

Claims 10, 13-15, 39-50, and 72-76 are pending in the application. Claims 1-9, 11-12, 16-38, and 51-72 are canceled. Claims 10, 43, 72, 74 are amended. Support for these amendments can be found throughout the specification. Accordingly, no new material has been added.

35 U.S.C. §112, First Paragraph, Written Description

Claims 10, 13-15, 39-42, 72, and 74-74 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states “claims 10, 13-15, 39-42, and 73 are method claims reliant upon the identity of the 5’ regulatory regions of SEQ ID NO:3. The sequence of SEQ ID NO: 3 is a coding sequence. As stated in the previous Office Action, a statement that the invention includes anti-sense nucleic acids complementary to the 5’ regulatory regions of HAAH and a signal peptide is insufficient to describe said regulatory region.” (*see page 2 of office action*)

Claims 10, 43, 72, and 73 are amended. The amended claim 10, for example, recites, “said compound is a nucleic acid comprising an antisense sequence which is complementary to the 5’ portion of the AAH sequence comprising cggaccgtgca of SEQ ID NO:3.” As such, the rejection is moot and should be withdrawn.

35 U.S.C. §112, First Paragraph, Enablement

Claims 10, 13-15, 39-50, and 72-76 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the instant claims are “directed to the anti-sense modulation of the human AAH, and read on the inhibition of tumor growth in a human patient by the administration of a nucleic acid vector which transcribes a polynucleotide which is complementary of the HAAH regulatory coding sequence, which is not disclosed.”

Claims 10, 43, 72, and 73 are amended. The amended claim 10, for example, recites, “said compound is a nucleic acid comprising an antisense sequence which is complementary to the 5’ portion of the AAH sequence comprising cggaccgtgca of SEQ ID NO:3.” As such, this aspect of the rejection is moot and should be withdrawn.

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The Examiner further states:

The specification is not enabling for the claims requiring the inhibition of tumor growth in a mammal, which reads on the treatment of a human patient with a naturally occurring tumor....The specification does not provide dosage or data for administering a therapeutically effective dosage of the complementary sequences of the regulatory regions of SEQ ID NO:3, or SEQ ID NO:3 itself, to tumor cells which would result in the inhibition of growth, reproduction, or survival of cancer cells. It is noted that many antisense therapies which appear to be promising using transfection *in vitro*, fail to provide any therapeutic efficacy when administered *in vivo*.

The Examiner cites the articles of Oza, Cripps, Tolcher and Marshall, as supporting her position, which is, in essence, that antisense therapy is in uncharted waters, that there is no correlation ("no absolute nexus") between *in vitro* systems or *in vivo* animal models, and actual treatment in a human. The Examiner stakes her position heavily on a perceived issue regarding the adequate delivery of antisense molecules to the tumor itself as well as to intracellular delivery of the molecule, and thus the ability to have any effect on tumor inhibition.

The invention is based on the target molecule, AAH, to which the therapy is directed, not a delivery method *per se*. Delivery of the composition to a desired target tissue site is common to all antisense protocols and, as also stated in the specification, adequate delivery methods and vehicles are known in the art and well within the bounds of routine methodology for the skilled artisan. Nevertheless, each cited reference is discussed in turn below.

Tolcher et al. is cited for teaching that the administration of ISIS 3521 and ISIS 5132 did not show any anti-tumor activity in patients with hormone-refractory prostate cancer (HRPC), even though these antisense drugs were previously shown to be active in Phase I studies (not "human tumor models" as phrased by the Examiner). This interpretation of Tolcher is not correct. In light of successful Phase I studies with ISIS 3521 and 5132, Tolcher et al. chose to test these drugs in HRPC patients, because HRPC is known to be 'intrinsically chemotherapy-resistant' and thus in need of new therapeutic agents. In Tolcher's randomized Phase II study, they found no significant success for either 3521 or 5132. Tolcher's hypothesis that this may have been the result because the known inhibitory action of 5132 and 3521 on the enzymes upon which they act (PKC-alpha and c-Raf kinase, respectively), alone, is insufficient for significant tumor regression in HRPC patients. Tolcher did not state or suggest that the lack of success in this study had anything to do with any aspect of delivery to the tumor cells and/or internalization.

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The Examiner states that Cripps et al. also teach that these same antisense molecules were ineffective in patients with metastatic colorectal cancer. Advanced or metastatic colorectal cancer is also very resistant to therapy, as noted by Cripps. Moreover, contrary to the Examiner's statements in the Office Action, Cripps states that it is possible that adequate levels were in fact achieved at the tumor sites. In discussing lack of efficacy, Cripps suggests two possibilities: that these molecules may not reach sufficient levels in the target tissue of this disease, or that adequate levels are achieved, but the targets are not relevant for this disease; or that unknown intracellular events prevented inhibition by the drugs in an effective manner. Cripps did not teach that either of these drugs is ineffective because they do not reach the target tissue/enzymes.

Marshall is cited by the Examiner as allegedly teaching that administration of ISIS 3521 to patients with metastatic colorectal cancer was largely unsuccessful, and that analysis of tumor biopsies showed minimal uptake of the antisense compound. This is also misconstrued by the Examiner. A reading of the entire article would reveal that the results confirmed that ISIS 3521 enters into the tumor environment and enters the tumor cells, and thus Marshall proposed to explain lack of success in one of two ways. First, they did find that PKC-alpha, the target, was overexpressed in colorectal cancer; however they did not have a baseline of non-malignant colon tissue to compare to, making their measurements irrelevant. Second, their lack of finding any significant change in tumors may have been because the downstream molecular events were 'too complicated' to measure the correct endpoints for the study. In other words, Marshall simply had no results, because he didn't measure the events in a comparative manner, and otherwise did not know what to measure. Again, there was no conclusion or suggestion that this antisense molecule did not work due to poor delivery to the tumor cells.

Finally, the Examiner states that Oza et al. teach that ISIS 5132 produced no response in patients with refractory/recurrent ovarian cancer. Once again, however, Oza does not disclose or suggest that this resulted from ineffective delivery of the antisense molecule to the target. Rather, Oza teaches that refractory/recurrent ovarian cancer is very resistant to therapy as an initial consideration. Oza only suggests an explanation for non-responsiveness that, as a single agent, and in this particular population of patients, the effects of ISIS 5132 may just not work. There is no teaching or disclosure that ISIS 5132 failed in this study to inhibit this type of ovarian cancer because it fails to reach the tumor or get internalized in the tumor cells.

In response to Applicants' previous remarks concerning the fact that efficacy has been shown in an art recognized model of human cancer (and taking into consideration the Declarations of Dr. Wands), the Examiner states such evidence is not persuasive, because "animal tumor models do not mimic the situation of a patient with a naturally occurring tumor." If such a position were to stand, no therapeutic agents for cancer would have or should be patentable unless shown to work in human clinical trials first. Statutory law, federal regulations, and procedural rules of patent law are contrary to this position.

Under MPEP 2107.03(III), entitled, "Data from in vitro or animal testing is generally sufficient to support therapeutic utility," it is stated, "...the court held that utility for a genus was found to be supported through a showing of utility for one species. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials." Applicants have provided data showing the efficacy of the claimed invention *in vitro* and *in vivo* using art-recognized animal models. Applicants have further supplied evidence that within the art antisense oligonucleotides have worked in as therapeutics, and have demonstrated by declaratory evidence that at least one species of the genus of antisense oligonucleotides is effective as claimed. Applicants are not required to prove efficacy in human subjects as a condition for allowance.

The patent law does not require "absolute nexus". The specification as filed together with the data and declaration of Jack Wands (22 Nov 2004), for instance, is sufficient evidence to establish that the invention is enabled. The Examiner has not provided evidence or grounds to suggest otherwise.

Moreover, the disclosure regarding the dosage of antisense oligonucleotide specified by Applicants in the instant application is sufficient for one skilled in the art to similarly formulate an adequate pharmaceutically deliverable composition of the antisense oligonucleotide. Thus, the specification provides sufficient disclosure of dosage forms. The specification further discloses a wide variety of methods of delivering antisense oligonucleotides to a patient. The following is an excerpt from the specification, page 18, lines 17-20, as well as the paragraph bridging paragraph to page 19:

"Antisense therapy is carried out by administering to a patient an antisense nucleic acid by standard vectors and/or gene delivery systems. Suitable gene delivery systems may include liposomes, receptor-mediated delivery systems, naked DNA, and viral vectors such as herpes viruses, retroviruses, adenoviruses and adeno-

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associated viruses, among others..... Parenteral administration, such as intravenous, subcutaneous, intramuscular, and intraperitoneal delivery routes, may be used to deliver nucleic acids or HAAH-inhibitory peptides or non-peptide compounds. For treatment of CNS tumors, direct infusion into cerebrospinal fluid is useful. The blood-brain barrier may be compromised in cancer patients, allowing systemically administered drugs to pass through the barrier into the CNS. Liposome formulations of therapeutic compounds may also facilitate passage across the blood-brain barrier.”

It is therefore respectfully submitted that the Examiner’s basis for finding lack of enablement of the above claims, specifically on a faulty interpretation of the art cited as being due to inherent problems of drug delivery, is inadequate to sustain this rejection. With regard to dosage regimens, the specification provides a level of guidance (p.13, line 27 to p. 15, line 19) that is sufficient for one of skill in the art to carry out the claimed methods.

Accordingly, reconsideration and withdrawal of this rejection are deemed proper and are earnestly requested.

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CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If the Examiner believes any issues remain that could be resolved by a telephone conference, she is invited to contact the undersigned at the number listed below.

A Petition for Extension of Time accompanies this paper.

Respectfully submitted,

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